# Thalamic Structure and Function In Youth with and at Familial Risk for Bipolar Disorder

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## INTRODUCTION

Metholodological Question: **How can we translate neuroimaging findings in carefully phenotyped groups into clinical trial designs?**

Youth with and at risk for bipolar disorder (BD) have early and specific neural network dysfunction while processing rewards. Here, we compared brain circuitry underlying monetary reward processing in youth with and at risk for bipolar disorder relative to youth at risk for depression and low-risk controls without any family history of any psychiatric disorders.

The goal was to examine brain circuitry differences and their association with key symptom dimensions related to aberrant goal pursuit.

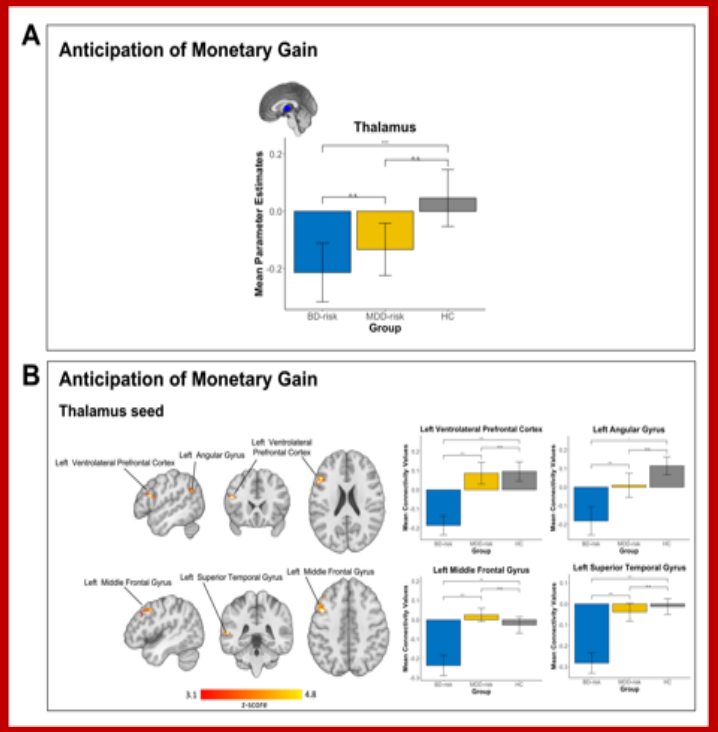
Youth with and at familial risk for bipolar disorder seem to have aberrant thalamic structure, function, and connectivity associated with trait and state features of bipolar disorder before and around emergent mania.

## METHOD

Youth with (n=22) versus without (n=23) BD received structural MRI scans at baseline and 12 months.

Healthy youth at high and low familial risk for mood disorders [BD-risk (n=40), MDD-risk (n=41), and HC (n=45) [mean age 13.09 +/- 2.58, 56.3% female] underwent functional MRI during reward processing using the monetary incentive delay (MID) task at baseline and were followed for behavioral and clinical outcomes over 4.37 +/- 2.29 years. Region of interest (ROI) analyses were conducted using an anatomically defined thalamus seed during reward anticipation and feedback. Psychophysiological interaction were also conducted to assess for task-related regional connectivity using the thalamus as a seed region ($Z > 3.1$; FWE-cluster corrected $p < .05$).We also used machine learning (ML) techniques (Support Vector Machine (SVM) and Random Forest) to evaluate whether neural correlates during reward processing with additional features could predict risk group membership.

**Youth with bipolar disorder have reductions in thalamic volume and youth at familial risk for bipolar disorder have decreased thalamic activation while anticipating monetary reward compared to healthy youth.**

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## RESULTS

Relative to HCs, adolescents with BD showed greater reductions in thalamic volume from baseline to 12-month follow up (Treatment x time interaction, Left thalamus: $F(45)=8.38$, $p =0.006$; Right thalamus: $F(45)=3.96$, $p =.05$). Reductions were negatively associated with mania symptom improvement in BD youth ($p<0.05$).

Relative to MDD-risk and HCs, BD-risk had decreased thalamic activation while anticipating monetary reward; $F(2,118) = 4.64$; $p = .01$ (FDR-corrected $p = .04$). BD-risk had less connectivity between the thalamus and left middle frontal gyrus ($Z > 3.1$; $p < .001$) and left superior temporal gyrus ($Z > 3.1$; $p < .05$) compared to MDD-risk. Decreased thalamic connectivity was associated with increased impulsivity at baseline and reduced prosocial behavior at 4-year follow-up. Thalamic function predicted group status with 67% accuracy (SD=8%).

## DISCUSSION

Thalamic Volume reductions may represent a disorder-related phenomenon. Reduced thalamic activation and connectivity during reward processing may represent early risk markers and may herald social dysfunction later in development.

Targeting thalamic function may inform a novel pharmacological lead, may inform novel outcomes for comparative effectiveness trials of existing drugs, define mediators and moderators, and inform stratification based on neurobiological risk.

**References**

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